REMARKS/ARGUMENTS

By the present Amendment, claims 1-5, 24, 25, and 42-44 are pending in this application. Claims 6-23, 26-41, and 45-59 are withdrawn as being directed towards non-elected subject matter. Applicants reserve the right to file one or more continuation, continuation-in-part or divisional applications towards any withdrawn subject matter. Claims 1, 24, and 25 are amended herein. These amendments correct obvious typographical errors. Basis for these amendments may be found throughout the specification and claims as originally filed. No new matter has been added.

Claim Rejections - 35 U.S.C. § 112

Claims 1-5, 24, 25, 42, 43 and 44 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. It is alleged that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention.

Applicants respectfully disagree and submit that the specification as originally filed provides sufficient enablement to one of skill in the art to make and/or use the claimed invention without undue experimentation.

First, several different examples of the claimed compounds having formula I are described in the specification. Beginning at paragraph [0124], the specification describes seven different compounds wherein R_1 is an alkyl ($-CH_2CH_3$, $-CH_2CH_2CH_3$, or $-(CH_2)_4CH_3$); R_2 is hydrogen, alkyl ($-CH_3$ or $-CF_3$), halogen (Cl or I), or alkoxy ($-OCH_3$); and R_3 is alkyl ($-CH_3$ or $-CF_3$), halogen (Cl or I), alkoxy ($-OCH_3$); acetyl ($-C{=}OCH_3$), or nitro ($-NO_2$). The as-filed specification further discloses at paragraphs [0256] to [0261], that the compounds of the invention can be readily prepared using known synthetic methodology, including using

combinatorial chemistry for generating libraries of these compounds. The as-filed specification also provides a number of journal articles and U.S. Patents that describe procedures for preparing these compounds, including, but not limited to Blondelle et al., Trends Anal. Chem. 14:83 (1995); the Affymax U.S. Pat. Nos. 5,359,115 and 5,362,899: the Ellman U.S. Pat. No. 5,288,514: the Still et al. PCT publication WO 94/08051; the ArQule U.S. Pat. Nos. 5,736,412 and 5,712,171; Chen et al., JACS 116:2661 (1994); Kerr et al., JACS 115:252 (1993); PCT publications WO92/10092, WO93/09668 and WO91/07087; Lerner et al. PCT publication WO93/20242; and Still et al. PCT publication WO 94/08051.

The Examiner contends that no data or results have been disclosed with regard to any biological or chemical assays in terms of efficacy of the claimed compounds on the claimed diseases or on inhibiting activation of signaling pathways such as the Hedgehog pathway. Applicants respectfully submit that the instant claims are composition claims. Further, the instant claims do not recite the treatment of any disease or pathology. In contrast, Applicants submit that the as-filed specification provides sufficiently detailed guidance to prepare and deliver the compounds to subjects in need thereof (see, for example, paragraphs 236-255). Moreover, a number of different assays for evaluating the activity of the claimed compounds of formula I are described in the specification, particularly at paragraphs [0262] to [0270]. Clearly, one having skill in the art would not encounter any undue experimentation in making and using the presently claimed compounds of formula I.

Furthermore, enablement of the claimed compositions does not require a demonstration that the invention may be used therapeutically. Applicants submit that the Federal Circuit has clearly established that human clinical data sufficient to gain FDA approval is not required to establish patentability. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). The Court continued by stating that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to

humans." Id. at 1568. Applicants also note that the rejection described in *In re Brana* was made under Section 112 and not under Section 101.

Applicants submit that in view of the as-filed disclosure, one having ordinary skill in the art would not encounter any undue experimentation in making and using the entire breadth of the presently claimed compounds and compositions. Accordingly, Applicants submit that the as-filed specification fully enables the presently claimed invention. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Claims 24, 42, 43, and 44 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hcaplus 1999:48617 (Reference U: WO 99/01127 and/or U.S. Patent No. 6,515,027) in view of Patani et al. (Reference V: Chem. Rev. 1996, 3147-3176). It is alleged that it would have been obvious to one of ordinary skill in the art to modify the prior art compounds to structurally similar compounds that are bioisosteres of one another.

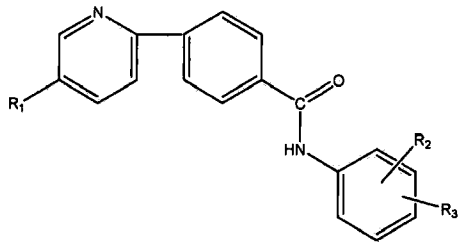
Applicants respectfully traverse this basis for rejection and submit that the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention. The Action fails to provide a sufficient basis for one having ordinary skill in the art to predictably arrive at the presently claimed invention with any reasonable expectation of success. Moreover, Applicants submit that the Examiner has used impermissible hindsight to reconstruct the presently claimed compounds.

At a minimum, it must be demonstrated that the cited references provide a sufficient basis to predictably arrive at the presently claimed invention, and even assuming, *arguendo*, that the cited references teach each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex, Inc.*, No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) ("A patent

composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art").

In the instant case, the Action has not provided sufficient rationale to support why the prior art would have led the skilled artisan to modify the prior art compounds identified by the Examiner and arrive at the presently claimed compounds with any reasonable expectation of success.

The presently claimed invention, as defined by the claims, distinguishes over the cited references by claiming a compound having the structure (I):



(I)

wherein R_1, R_2 and R_3 are as claimed.

Hcaplus 1999:48617 does not teach or suggest any such compounds. Instead, this reference teaches substituted benzanilides, which are ligands, agonists or antagonists of the CC chemokine receptor CC-CKR5, now designated as the CCR5 receptor. This reference teaches that the disclosed compounds selectively inhibit the CCR5 receptor and therefore, are useful for treating asthma and atopic disorders, rheumatoid arthritis, sarcoidosis and other fibrotic diseases, atherosclerosis, psoriasis, autoimmune diseases such as multiple sclerosis and inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), and HIV infection. This reference, however, does not teach or suggest any of the presently claimed compounds having structure (I).

The Action alleges that the difference between the prior art compounds and the instantly claimed compounds is the teaching of a phenyl ring in the prior art as a replacement of the pyridyl ring in the instant compounds. The Action further alleges that one having skill in the art would be motivated to modify the phenyl group (ethylated) of the compounds of Hcaplus 1999:48617 with pyridyl groups (ethylated) as presently claimed, because Patani et al. allegedly teaches that phenyl and pyridyl rings are bioisosteric replacements of one another that result in retention of biological activity within different series of pharmacological agents. Applicants respectfully disagree.

Applicants respectfully submit that Patani et al. teaches that bioisosteres elicit similar biological activity due to common physiochemical properties (see p.3148, second paragraph). Patani et al. provides numerous examples of bioisosteric groups that are considered equivalents in particular compounds. Nowhere in the entirety of the Patani et al. reference is it suggested that any bioisosteric substitution would be effective in all instances. Regarding pyridyl/phenyl bioisosteres, Patani et al. merely provides two examples of antihistamine drug design wherein a pyridyl ring was substituted for a phenyl ring, but does not offer any data or guidance showing the replacement of a substituted phenyl ring the presently claimed substituted pyridyl ring in a compound of formula (I) as presently claimed, nor in any other compounds.

Applicants respectfully submit that there is no reasonable basis to conclude that Patani et al. teach or suggest that **all drugs** comprising a substitution of a phenyl group for a pyridyl group at the same position would be bioisosteres of one another. One having skill in the art would appreciate that only particular positions of particular compounds would tolerate phenyl/pyridyl bioisosterism, and moreover, that it is not predictable which particular positions of which particular compounds would be tolerant, especially in the absence of any evidence to the contrary.

Moreover, Patani et al. fails to provide any guidance with regard to: i) choosing a particular bioisosteric group in a molecule over another bioisosteric group and ii) which group in

a molecule should be subjected to bioisosterism. Thus, Applicants further submit that the Action has not provided a sufficient basis for one having ordinary skill in the art to modify the ethyl substituted phenyl group of Hcaplus 1999:48617 with a pyridyl group rather than the other two phenyl groups present in the compounds of Hcaplus 1999:48617.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492. F.3d 1350 (Fed. Cir. 2007), the Court noted that "In addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)." Furthermore, the Court pointed to *In re Deuel,* 51 F.3d 1552, 1558 (Fed. Cir. 1995), where the Court stated that "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.*

The Court clarified, however, that in order to find a *prima facie* case of unpatentability in such instances, a showing that the "prior art would have suggested making the **specific molecular modifications necessary** to achieve the claimed invention" was also required. *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)).

The *Takeda* Court concluded that such a test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.

Furthermore, Applicants note that KSR does not advocate the use of hindsight. Particularly, the modification of one phenyl group over two others without any guidance, motivation, or suggestion to do so amounts to using impermissible hindsight to reconstruct Applicants' invention.

The KSR court noted that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See, Graham, 383 U. S., at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to 'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equip-ment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F. 2d 406, 412 (CA6 1964))). See also, e.g., *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (("[One] 'cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'") (quoting *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988)).

Applicants respectfully submit that the Action has clearly failed to provide a sufficient basis of rationale that would lead the skilled artisan to modify the prior art compounds Hcaplus 1999:48617 to arrive at the presently claimed compounds. Thus, Action has failed to establish a *prima facie* case of obviousness against the presently claimed compounds.

Accordingly, as the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention, Applicants respectfully request reconsideration and withdrawal of these bases for rejection.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

A request for a three-month extension of time under 37 CFR 1.136(a) accompanies this response. The Commissioner is hereby authorized to charge $555.00 as the fee for the three-month extension of time to Deposit Account No. 07-1896. No additional fees are believed to be due with the present communication, however, the Commissioner is hereby authorized to charge any fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-identified Attorney Docket Number.

Respectfully submitted,

Date: September 29, 2009

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